

subjective calculations of future reward rates in patients suffering from low mood.

The increasing prevalence of suffering from maladaptive mood regulation may reflect a mismatch between mood and modern environments. There has been a dramatic decrease in environmental risks, reflected by dropping rates of wars, homicides and numbers of dangerous animals. As a result, mood systems look more and more like sensitive and error-prone smoke detectors in a world where candles, fire heating and smoking have become out of fashion. Moreover, mood is not specific for a certain domain⁷. One cannot have at the same time a high mood at work and a low mood in the family. Mood is general, possibly because in ancient times reward opportunities were highly correlated. A flood destroyed almost all of them.

Another good example of a possible mood-environment mismatch is grief. In our ancestral environment, grief may have had the function to motivate searching for loved ones who simply did not return to the camp⁸. Nowadays, grief is mostly a response to a definitive loss in which prolonged sadness has become maladaptive. Vivid memories, hallucinated voices and felt presence of a meaningful other prepares for a costly and futile search. As a result, modern psychiatry has good reasons to develop therapeutic strategies for individuals suffering from prolonged grief.

Because the relationship between mood and environment is subjective, mostly unconscious and complex, psychiatry has the tendency to completely ignore this relationship. In the DSM-5, the environment does not play a role when diagnosing mood disorders. Low mood associated with symptoms such as anhedonia, low energy levels and negative thinking defines a major depressive episode. This diagnostic concept makes sense in an environment with a constantly high reward rate. However, not all environments on this planet comply with this description. Our diagnostic systems hold the danger of medicalizing real social and environmental problems. Dysthymia and mild depression may be an adaptive response to prolonged and realistically expected enduring adverse conditions. As a result, it is important for clinicians to carefully consider the individual life circumstances in which a mood disorder develops. Facing enduring adversity, therapy-induced optimism and mood enhancing drugs may increase the risk of physical and mental traumatization and even death².

Taken together, an evolutionary view helps to see mood as the product of interactions between neurobiological mechanisms and the structures we give to our societies and environments. Fava and Guidi's approach has the potential to identify these interactions and to foster the de-

velopment of individual therapeutic plans that correspond to them.

In Fava's well-being therapy, self-observation and structured diary help to identify complex influences of the environment on well-being over longer periods of time⁹. The focus on positive situations and euthymia allows for the identification of expected reward rates that are crucial for mood regulation. Balanced functioning, flexibility, adaptation, openness, stage-dependent learning, awareness, macro-analysis, acceptance, autonomy, growth and flourishing are the key words of this timely and promising approach.

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The untapped power of allostasis promoted by healthy lifestyles

Fava and Guidi¹ write: "Psychiatrists often consider the positive characteristics displayed by a patient in their clinical judgment; yet current assessment and treatment strategies are shifted on the side of psychological dysfunction". Similarly, the word "stress" is commonly used to emphasize the negative aspect of the experiences to which we adapt daily; and this is done in such a way as to implicate cortisol as responsible for negative consequences, without also recognizing the positive role of cortisol and other physiological mediators in promoting adaptation and maintaining health in response to all experiences, whether or not we call them "stressful".

Indeed, the word "stress" is used in several ways so as to make it ambiguous. "Good stress" involves our taking a chance on something we want, such as interviewing for a job or school, or giving a talk before strangers and feeling rewarded when we are successful. "Tolerable stress" means that something bad happens, like losing a job or death of a loved one, but we have the personal resources and support systems to weather the storm. "Toxic stress" means that, when something bad happens, we do not have the personal resources or support systems, and, as a consequence, we lack a sense that we have some control. We may then suffer mental and physical health problems over time, particularly if the situation

is not resolved.

Now, let us put these three forms of "stress" into a biological and behavioral context. We know that "homeostasis" means the physiological state which the body maintains to keep us alive – that is, body temperature and pH within a narrow range, and adequate oxygen level. In order to maintain homeostasis, our body activates hormone secretion as well as the autonomic and central nervous system to help us adapt, for example, when we get out of bed in the morning, walk up a flight of stairs, or have a conversation. These systems are also turned on when we are surprised by something unexpected, or get into an argument, or run to catch a train.

Using the word “stress” does not really recognize all of the underlying biology, while the word “allostasis” focuses on the active process of adaptation to many challenges, whether not we call them stressful². “Allostatic load” is a term that refers to the cumulative changes in the body and brain that are produced by dysregulation and overuse of the “mediators” of allostasis^{2,3}.

The basic concept behind allostatic load is an outgrowth of Sapolsky’s “glucocorticoid cascade hypothesis” of stress and aging⁴, that was broadened to encompass not only glucocorticoids but also other interacting mediators of adaptation, and to include protective/adaptive as well as damaging effects of those mediators.

The “mediators” help us adapt as long as they are turned on in a balanced way when we need them, and then turned off again when the challenge is over. When that does not happen, they can cause unhealthy changes in brain and body. This is also the case when they are not produced in an orchestrated and balanced manner – for example, too much or too little cortisol or an elevated or too low blood pressure – leading over weeks and months to “allostatic load”. When the wear and tear is strongest, we call it allostatic overload, and this is what is occurring in toxic stress⁵. An example is when hypertension leads to a heart attack or stroke and abdominal fat contributes chemicals that accelerate the coronary artery blockade and increase stroke risk.

One essential aspect of allostasis and allostatic load/overload is how the brain responds. We now know that genes are turned on and off epigenetically by experiences over the life course⁶, and that there is an adaptive structural plasticity of synapses, some of which are eliminated while others are formed during the daily circadian day-night cycle, as well as following acute and chronic stressors⁷.

The dendrites of neurons in brain ar-

eas such as the hippocampus, prefrontal cortex, amygdala and nucleus accumbens can shrink or grow and become less or more branched as a result of experiences, including those referred to as “stressful”. A healthy brain shows resilience and recovery after the stressful experience is over. Yet, after a stroke, head trauma or seizure, there can be permanent irreversible damage and neuron loss due to allostatic overload, involving excitatory amino acids, cortisol and other mediators. Nevertheless, after a stroke, compensatory brain plasticity can help reduce the damage⁸.

How does this relate to euthymia and positive aspects of health? Fava and Guidi state: “The findings indicate that flourishing and resilience can be promoted by specific interventions leading to a positive evaluation of one’s self, a sense of continuing growth and development”. Moreover, they emphasize that the pursuit of euthymia is not a therapeutic intervention for specific mental disorders, but a trans-diagnostic strategy to be incorporated in an individualized therapeutic plan. Here, plasticity and resilience of the brain is essential.

Translated into the language of stress biology, euthymia means using allostasis optimally and maintaining a healthy balance that promotes positive aspects of brain and body health through health-promoting behaviors. These behaviors involve not only diet, but also adequate and good quality sleep, positive social interactions, as well as a positive physical environment that is safe and includes green space, all of which reduce allostatic load. Regular physical activity benefits the brain as well as the body and does so, at least in part, by increasing generation of new neurons in the hippocampus and, as a result, counteracting depression and improving aspects of memory. These basic health-promoting behaviors that promote allostasis can help the self-healing process, since the inherent adaptive plas-

ticity of the brain can operate more effectively.

But the most provocative and far-reaching implication, even beyond euthymia, is the reported physiological difference between an eudaimonic lifestyle involving meaning and purpose and an hedonic lifestyle involving seeking and finding pleasure. According to Fredrickson et al⁹, people with an hedonic lifestyle show in their white blood cells a higher expression of pro-inflammatory genes and a decreased expression of genes involved in antibody synthesis and type I interferon response, compared to those with a eudaimonic lifestyle, who show the reverse⁹ and thus a lower allostatic load.

Fredrickson et al go on to suggest that hedonic and eudaimonic lifestyles engage different gene regulatory programs, despite their similar effects on total well-being and depressive symptoms. They argue that “the human genome may be more sensitive to qualitative variations in well-being than are our conscious affective experiences”. Clearly, this provocative idea requires an even deeper exploration of those aspects of psychological well-being, positive thinking and euthymia than is currently available.

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Euthymia and disabling health conditions

The focus of positive psychology can be seen as an attempt to address the philosophical question first put forth by the

ancient Greeks: “what does it mean to live a good life?”. When people’s physical body changes and the person-environ-

ment interaction significantly alters due to a chronic illness/disability condition, this question can take on additional di-